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INSULIN-FREE PANCREATIC EXTRACT AND THE CIRCULATORY HORMONE (KALLIKREIN OF FREY AND KRAUT)*

A COMPARATIVE STUDY OF THEIR EFFECTS ON ANGINA PECTORIS

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DISCUSSION *by H. O. Koefod, M. D., Santa Barbara; Hans Lisser, M. D., San Francisco.*

IN 1920, Pribram and Herrnheiser,[1] studying the nondialysable fraction of human urine, found that it caused a fall in blood pressure on injection into the rabbit. Eight years later, Prof. E. K. Frey, chief of the Sub-surgical Clinic of the Medical Academy of Düsseldorf, and his coworkers described the properties of a vasodilator substance recovered from the urine, which he now regards as a hormone and which he has named Kallikrein. This principle exerts a regulatory function upon the distribution of the circulating blood, dilating the arterioles of the brain, lungs, skin and muscles[2] with resultant fall in blood pressure. Elaborated in the pancreas, it exists normally in the circulating blood in combination with an inactivator, a polypeptide probably produced in the lymph glands, and is released by change of pH to the acid side.[3,4] It is secreted into the urine in an active form where it may be recognized by a typical reaction on intravenous injection into the experimental animal, namely, a fall in blood pressure and an increase in amplitude of cardiac contraction.[5] Frey states that, when calibrated in dog units by this latter effect, one unit is contained in 3 to 5 cubic centimeters of human urine and 2 to 20 cubic centimeters of blood.[2] Chemically and physiologically this substance is distinct from histamin, cholin, purine bodies and other hormones.[5]

This substance has received extensive clinical trial on the Continent in the treatment of angiospastic disease with, to date, rather conflicting results. The literature is too large to be reviewed in detail. Favorable results have been reported in the treatment of essential hypertension,[6,7,8] angiospastic gangrene and intermittent claudication.[9,10,11] In angina pectoris, the available studies are conflicting, but Frey[9] and Leschke,[7] who have had the most experience with this method of therapy, have secured a favorable response in some cases, which Singer[12] attributes to a foreign protein reaction.

In 1929, Vaquez, Giroux, and Kisthinios[13] reported remarkable results in a series of twenty patients having angina pectoris treated with an insulin-free extract of pancreas whose physiologic activity had been studied by Gley and Kisthinios. These workers[14] prepared an extract which contains a heat-stable depressor principle, an adrenalin antagonist, which was found, upon intramuscular injection, to so ameliorate the anginal syndrome that Vaquez considered this method of treatment superior to other measures. He attributed the results to a trophic action upon the blood vessels. Numerous confirmatory reports have since appeared in the foreign literature[7,15,16,17] and one in this country.[18]

We have been studying these substances since 1930. Pharmacologic investigations, published in detail elsewhere,[19] may be summarized here. The extract of pancreas dilates the coronary arteries of the perfused heart of a rabbit to a greater degree than that produced by the most active of the purine derivatives, theophyllin ethylenediamin. The circulatory hormone (Kallikrein) is likewise a coronary dilator, but is somewhat more feeble than the pancreatic extract as compared on the basis of hypotensive activity.

The pressor effect in the rabbit of intravenously injected adrenalin may be inhibited by both of these substances. This is a constant attribute of the circulatory hormone, Kallikrein, but the adrenalin antagonism exerted by different batches of pancreatic extract is extremely variable. While we have been unable to produce the typical increase in cardiac contraction with any lot of pancreatic extract yet tested, it seems likely that the adrenalin antagonism exerted by some of the samples may be due to an inconstant content of circulatory hormone. The latter also protects the rabbit from lethal doses of intravenous adrenalin, but this protection is not afforded the rat. It is an interesting observation that the effect of ad-

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renalin upon the carbohydrate metabolism, as measured by hyperglycemia, is not influenced by the hormone.

Our attempts to identify the active principles of these preparations have not met with success. It has been suggested [18] that the pancreatic extract contains adenylic acid or adenosin, derivatives of nucleic acid which are depressor substances and coronary dilators. We have been unable to demonstrate their presence in these preparations by either biologic or chemical methods (data to be published).

In summary, we feel that, while the extract of pancreas may contain circulatory hormone, there is present, in addition, another substance, or substances, upon which, in part at least, its therapeutic activity may depend.

CLINICAL

In 1931, we reported the results of treatment with pancreatic extract obtained in twenty patients with angina pectoris.[20] A control series of forty patients, treated by the usual medical measures, was also studied. The extract was given intramuscularly in a dosage of from 30 to 60 hypotensive units on alternate days, or twice weekly, for a total of from ten to twenty injections. The course of injections was repeated a second or even a third time, if results were not apparent after the first series. The average follow-up period was 6.7 months, varying from 1 to 13 months. Two, or 10 per cent, of these patients were refractory; 25 per cent were somewhat relieved; 55 per cent were greatly helped, and two, who had been benefited, died later while under observation. These results were noticeably better than those obtained in the control group. The anginal attacks frequently ceased during or after the injections in the patients responding. In some instances this improvement persisted as long as six months. The response to treatment was nearly as good in instances of long-standing severe angina as in those patients suffering less severe seizures, and appeared to be quite independent of the presence of myocardial damage as shown in the electrocardiogram. Incidentally, we could not demonstrate any change in the latter as the result of treatment, nor was the blood pressure noticeably altered in those patients with hypertension.

It has been possible to follow to the present time fifteen of these twenty patients treated with pancreatic extract. Three have died—one from cardiac decompensation, one from a ruptured appendix, and one as the result of a coronary occlusion. The anginal attacks returned in four of the remaining patients and were not influenced by further exhibition of the extract. Another patient, previously reported as refractory to the treatment, has remained so on further trial. In seven patients the original improvement has been maintained. Four of these had a severe type of angina initially, of whom three had electrocardiographic evidence of myocardial damage. Two had attacks of moderate frequency and severity; one suffered from mild seizures. This, together with further use of the extract, has strengthened us in our opinion that hypodermically given pancreatic extract offers an addition of value to the therapy of angina pectoris.

CIRCULATORY HORMONE

During the past year, Dr. Fritz Bischoff, working in the Cottage Hospital laboratory, has been able to supply us with a limited quantity of a concentrated preparation of this substance. The method of preparation will be published elsewhere. We have treated ten carefully studied patients having angina pectoris with this preparation, and in a number of them have been able to compare its effects with those resulting from an exhibition of the extract of pancreas. The substance has been given intramuscularly daily, or on alternate days, in a dosage varying from 50 to 250 units (a unit being the amount which, injected into the jugular vein of a grown rabbit, is just sufficient to cause a fall in blood pressure and an increase in pulse amplitude of from three to four minutes' duration). There are no toxic effects, but in several patients a nonspecific protein reaction resulted which was subsequently obviated by initially graded small doses.

The group consisted of five females with an average age of fifty-nine years, and five males with an average age of sixty-five years. Hypertension was present in three of the females. The blood Wassermann reaction was negative in every instance. There was electrocardiographic evidence of myocardial damage in five patients.

Five of the patients received the circulatory hormone alone in a total dosage of from 600 to 4,500 units. Two patients were apparently benefited, but in one, a woman, the psychic element may well have been responsible. The other patient, a man seventy-seven years of age, with an angina of sixteen years' duration, has returned to his business, and has decreased his nitroglycerin intake from that of two to three tablets a day to one or two a week. However, he has been followed for only several weeks. The remaining five patients received both preparations, the hormone Kallikrein and the pancreatic extract. One patient died without receiving benefit. Two patients, after receiving extract of pancreas, were free of attacks for periods of three and seven months, respectively. Upon return of symptoms, they were given the circulatory hormone with apparent relief, but the follow-up observation has been relatively short. The two remaining patients are of particular interest. They received, respectively, 1,540 to 2,500 units of the hormone Kallikrein over periods of two and four weeks without benefit. They were then given the extract of pancreas. One patient suffered no further seizures after the sixth injection and has remained symptom-free to the time of writing, a period of two months. The other patient, who had previously had a coronary occlusion with a resultant incapacitating angina pectoris, likewise experienced immediate relief, and is completing her course of injections at the present time.

COMMENT

The laboratory evidence which indicates that the extract of pancreas is not dependent upon a content of circulatory hormone to explain its activity has been reviewed. We believe that the foregoing clinical experiences strengthen this assumption, but by no means prove it. Our series of patients treated with the hormone is small. We do not wish to draw the definite conclusion that this substance will prove valueless in the treatment of angina pectoris, but we believe that its primary field of usefulness will lie elsewhere. The extract of pancreas is, in our opinion, of definite value, and we recommend its trial, particularly in those patients who are not relieved by other measures.

SUMMARY

1. The physiologic properties of an insulin-free extract of pancreas and of the circulatory hormone (Kallikrein) are briefly reviewed.

2. Evidence is adduced which indicates that the pancreatic extract is not dependent upon a content of the hormone to explain its entire activity.

3. Experiences with the use of pancreatic extract in the treatment of angina pectoris are described. Favorable follow-up observations on a previously reported series of cases are given.

4. The results obtained by the use of both preparations in a small series of cases indicate that the circulatory hormone will prove ineffective in many instances, whereas an exhibition of the pancreatic extract may give beneficial results.

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DISCUSSION

H. O. Koefod, M. D. (1421 State Street, Santa Barbara).—I believe it can be conservatively stated that insulin-free pancreatic extract, now on the market under various trade names, is a distinct addition to our treatment of angina pectoris. With kallikrein, the substance obtained from urine, I have had no experience.

In a comparatively small series, while the amount of benefit has varied greatly, it has been definite in over one-third of the cases. In some it has been striking. In the perfused animal, it apparently brings about an increased and prolonged output through the coronary arteries by vasodilatation. It seems difficult to see how this can be the explanation in cases with markedly sclerosed coronary vessels, unless there is an added vasoconstrictor factor. There is clinically no suggestion of increased pressure within the aorta to account for the increased flow. To the possibility that the viscosity of the blood might in some way be changed, I have been unable to find any reference.

There is some question, however, as to the specificity of this substance. An extract with apparently similar action, and comparative results in the treatment of angina, has been prepared from voluntary muscle and other tissues.

Two of my first sixteen cases developed a coronary thrombosis while under treatment with pancreatic extract. This in all likelihood was coincidental. Doctor Wolffe and co-workers reported, in a paper published three years ago, the development of a coronary T-wave in two of twenty cases while under treatment. An elderly patient of mine with hypertension who did not respond to the pancreatic extract did well on euphyllin.

While I feel that the pancreatic extract is of distinct value, I believe it will require several years of clinical trial to find its true worth in the therapy of vascular disease.

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H. Lisser, M. D. (384 Post Street, San Francisco).—Doctors Nuzum and Elliot deserve great credit for their timely presentation of observations on these interesting extracts. Though condensed with commendable brevity, even a slight acquaintance with this sort of investigation reveals the considerable skill and labor involved, both in the preparation of these substances and in their careful clinical application.

The authors, when inviting the writer to participate in the discussion of their conservative paper, were aware of his very limited experience with these hormones, but no doubt included him because of his particular interest in clinical endocrinology. His com-

ments, therefore, cannot be directed to the immediate points they raised, but must be transposed into reflections on the wider implications of their thesis.

The astute observations initiated by Herrick many years ago have permitted an improved recognition of the significant distinctions differentiating angina pectoris and coronary occlusion. The latter condition, with its graver import, is based upon coronary vessel damage, whereas the former arises, presumably, from sympathetic spasm. This underlying pathologic difference demands a correspondingly different therapeutic approach.

It is altogether likely that a number of circulatory disorders, in addition to angina pectoris, have their origin in the common denominator of sympathetic sensitization or hypertonus. One need but mention intermittent claudication, Raynaud's disease, certain forms of gangrene, perhaps essential hypertension, and autonomic imbalance with vasomotor instability, as familiar varieties of angiospasm.

In the attempt to ameliorate or alleviate these vessel tightenings, resort has been had to a great number of drugs capable of producing some degree of vasodilatation. From most of these, merely transient pharmacodynamic effects have been obtained. The results achieved by Nuzum and Elliott and their predecessors, to whom they refer, seem, in some instances at least, to be of a more durable character; perhaps because body substances are utilized of which there may be a lack, with restoration of a more normal circulatory mechanism.

In recent years effort has been redirected, both medically and surgically, to a more specific and profound attack on the transmission lines of the sympathetic system itself, or at certain power houses, such as the adrenals, which store and release some of the stimulating energies of the network. Surgeons have performed such daring and novel maneuvers as ganglionectomies, nerve resections, adrenal denervations, and even adrenalectomy, followed at times by spectacular relief. One need but cite the prompt and complete cessation of violent attacks of paroxysmal hypertension by removal of an adrenal paraganglioma (cases of Mayo, Pincoffs and Shipley, Porter and Porter).

After all, it may turn out that angiospastic states occur because of an undue ascendency of the adrenal medullary stimulant adrenalin, due to a deficiency of its normal antagonists such as the circulatory hormone of Frey (kallikrein) or the insulin-free pancreatic extract. Now that two separate and differing extracts have been prepared from the posterior hypophysis, and two (with the probability of two or three more) from the anterior pituitary, it would not be surprising if a third extract, in addition to trypsin and insulin, were established for the pancreas. Also, since the anterior pituitary-like substance obtained from human pregnancy urine and human placenta may not be different and separate hormones from the sex hormones obtained directly from the prehypophysis itself, but merely altered in transit from gland to urine, so is it not likewise conceivable that the insulin-free pancreatic extract and the circulatory-urine extract kallikrein may be one and the same, but that the latter has slightly different chemical and physiologic properties because of modifications during transit? Many substances undergo chemical change from their site of origin to site of elimination.

It is to be hoped that greater quantities of these circulatory hormones will be available, and that their potency may be increased so that adequate clinical data may be accumulated. The duration of potency must be ascertained. To this end each batch must be retested periodically. No doubt some of the failures from the use of the commercial preparations can be ascribed to loss of potency. It would be unfortunate if this promising therapy were prematurely abandoned. Further reports from Doctors Nuzum and Elliot, and others, will be awaited with interest.

HYPERPYREXIA BATHS AND EPILEPSY*

THE CHEMICAL AND PHYSIOLOGIC RESPONSES OF THE BODY TO HYPERPYREXIA BATHS, AND THEIR SIGNIFICANCE IN THE EPILEPTIC SYNDROME

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DISCUSSION *by Samuel D. Ingham, M. D., Los Angeles; H. Douglas Eaton, M.D., Los Angeles; Thomas G. Inman, M. D., San Francisco.*

THE therapeutic use of hyperpyrexia baths has received increasing attention during recent years. The present state of knowledge concerning the underlying mechanism by which disease processes are influenced has not advanced, however, much beyond that of the ancients, who empirically discovered the healing properties of hydrotherapeutic measures many centuries ago.

Modern clinicians have pointed out the specific value of this measure and have directed attention to the febrile response of the body to hot baths as having special therapeutic significance. Many facts of practical importance have been added to the subject by the observations of Mehrtens and Pouppirt.[1,2]

Investigation along chemical and physiologic lines has revealed that the protective adjustments set into motion within the body upon exposure to high environmental temperatures are of such a magnitude as to be detected without difficulty, and of a quality as to directly alter the state of functional activity of the nervous system. Objective evidence for the latter assumption is found in the frequently observed clinical signs of tetany and of major convulsive seizures in epileptics during the course of hyperpyrexia baths.

The present discussion will bring to mind briefly the more prominent disturbances in chemical and physiologic equilibrium instituted by hot baths, and will attempt to correlate these changes with their apparent effect upon the convulsive tendency in patients presenting the epileptic syndrome.

SYMPTOMATOLOGY OF HYPERPYREXIA BATHS

A definite train of subjective and objective symptoms develops upon exposure of the human body to high temperature environments. These have been studied and well described by a group of careful observers.[3 to 10] The appearance of frank tetany in a certain number of subjects, and of convulsive reactions in many cases of epilepsy and general paresis, has led to a search for a possible explanation of these phenomena. Other neurological findings have been elicited under the influence of hyperpyrexia baths, to the end that localization of central nervous system pathology has been accomplished in a few cases. Temporary psychic disturbances have also been observed. Currie [11] described the abnormal symptomatology developed in baths of 105 degrees Fahrenheit in 1797, and advised strongly against temperatures above 100 degrees Fahrenheit.

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